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WO 03/053989 A1

(54) Title: MASKED PHOSPHATE CONTAINING NUCLEOSIDE DERIVATIVES AND THEIR USE AS ANTIVIRALS

(57) Abstract: A compound of general formula [masked phosphate] - [sugar] - B in which B is selected from an optionally substituted cyclopentyl, pyrrolyl, diazolyl, triazolyl, indenyl, indolyl, indazolyl or benzotriazolyl group or a pharmaceutically acceptable derivative or metabolite thereof, and the compound in combination with a pharmaceutically acceptable excipient, pharmaceutical compositions containing the compound, the use of the compound in therapy/prophylaxis, for example where the use therapy/prophylaxis of viral infection, particularly in relation to infection by human immunodeficiency virus (HIV). Optional substituents for the compound include H, NO_2, CO, COR^{15}, OR^{15}, CN, O, $CON(R^{15})_2$, $COO\ R^{15}$, $SO_2\ R^{15}$, $SO_3\ R^{15}$, SR^{15}, NHCHO, $(CH_2)_n N(R^{15})_2$ or halogen where R^{15} is H or hydrocarbyl and n is 0, 1, 2, 3 or 4.

MASKED PHOSPHATE CONTAINING NUCLEOSIDE DERIVATIVES AND THEIR USE AS ANTIVIRALS

Field of the invention

The present invention relates to a particular class of nucleoside analogues and their therapeutic and prophylactic use, for example in the therapy and prophylaxis of viral infection, particularly in relation to infection by human immunodeficiency virus (HIV), the aetiological agent of acquired immunodeficiency syndrome (AIDS).

Background to the invention

There has been much interest in the use of nucleoside analogues as inhibitors of HIV. For example, 2',3'-dideoxy-2',3'- didehydrothymidine (d4T) and 3'-azido-3'-deoxythymidine (AZT) are both known inhibitors of the virus.

The inhibition of HIV by these, and other nucleoside analogues, appears to depend upon conversion of the nucleoside analogue *in vivo* to the corresponding 5'-triphosphate by endogenous kinase enzymes.

The absolute dependence upon endogenous host-cell kinases to mediate activation of administered antiviral nucleoside analogues places constraints upon the structures of nucleoside analogues which can be activated. Nucleoside analogues which fall outside these strict constraints will be inactive, even if their 5'-triphosphates are potent and selective inhibitors of a viral target, such as reverse transcriptase (RT).

Thus, the dependence upon endogenous host-cell kinases to mediate activation can lead to poor activity, the emergence of resistance, and clinical toxicity.

If nucleotides could be efficiently delivered intracellularly, the endogenous nucleoside kinase would be by-passed and the structural constraints such host enzymes impose would be obviated. In this way, wider structural variation of the nucleoside analogue would be permitted, and more specific (less toxic) inhibitors of viral function could be developed and exploited.

However, polar (charged) free nucleotides exhibit extremely poor membrane penetration.

This problem has been addressed by masking the phosphate group (McGuigan, C., Nicholls, S.R., O'Connor, T.J. and Kinchington, D. (1990) Synthesis of some novel dialkyl phosphate derivatives of 3'-modified nucleosides as potential anti-AIDS drugs. Antiviral Chem. Chemother. 1, 25-33). Here, inactive phosphate derivatives of the parent nucleoside analogue having "masked phosphates" penetrate the cell membrane and liberate the bio-active nucleotides intracellularly. In this way, the endogenous kinases have been by-passed

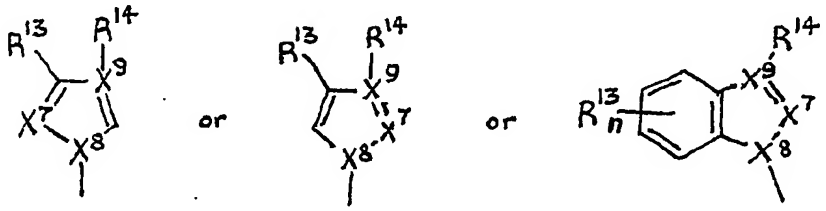
and delivery of nucleotide analogues intracellularly has been achieved using several highly modified 3'-substituted nucleosides (McGuigan, C., Kinchington, D., Wang, M.F., Nicholls, S.R., Nickson, C., Galpin, S., Jeffries, D.J. and O'Connor, T.J. (1993) Nucleoside analogues previously found to be inactive against HIV may be activated by simple chemical phosphorylation. FEBS Lett. 322, 249-252; McGuigan, C., Kinchington, D., Nicholls, S.R., Nickson, C. and O'Connor, T.J. (1993) Kinase bypass: a new strategy for anti-HIV drug design. BioMed. Chem. Lett. 3, 1207-1210).

This "kinase by-pass" approach is further developed in WO96/29336, which describes a particular class of nucleoside analogues having "masked phosphate" moieties. The analogues are highly potent viral inhibitors in both TX and TK+ cells, and yet retain activity against nucleoside (e.g. d4T) - resistant virus.

The masked phosphate kinase by-pass approach has now been extended to several nucleoside analogues which have modifications in the base region.

Summary of the Invention

According to the present invention there is provided a compound of general formula: [masked phosphate] - [sugar] – B, wherein B is



wherein X^7, X^8 and X^9 are the same or different and each is C or N, when X^9 is N then there is no R^{14} group;

R^{13} and R^{14} are the same or different and each is H, NO_2, CO, COR^{15}, OR^{15}, CN, O, $CON(R^{15})_2$, $COOR^{15}$, SO_2R^{15}, SO_3R^{15}, SR^{15}, NHCHO, $(CH_2)_nN(R^{15})_2$ or halogen;

R^{15} is H or hydrocarbyl;

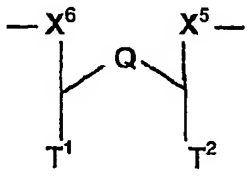
n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable derivative or metabolite thereof.

As used herein, the term "masked phosphate" means an analogue or derivative of a phosphate group which has been modified such that it is membrane permeable (i.e. can enter mammalian cells by crossing the cell membrane). Preferably, the masked phosphate groups comprise phosphoramidate derivatives (e.g. aryloxy phosphoramidates).

As used herein, the term "sugar" means any sugar (or sugar analogue) and includes natural sugars (such as ribose and deoxyribose) as well as non-natural sugars.

Preferably, the sugar moiety is



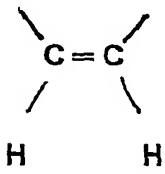
wherein

X^6 may be absent or is CH_2;

X^5 may be absent or is CH_2;

Q is selected from O, NR^6, S, CR^6R^7, CR^6W^3 and CW^3W^4 , where R^6 and R^7 are independently selected from hydrogen, alkyl and aryl groups; and W^3 and W^4 are heteroatoms;

T^1 and T^2 are independently selected from hydrogen and CH_2R^8, where R^8 is selected from H, OH and F; or T^1 and T^2 are linked together and together are selected from the groups:



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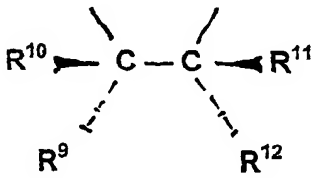
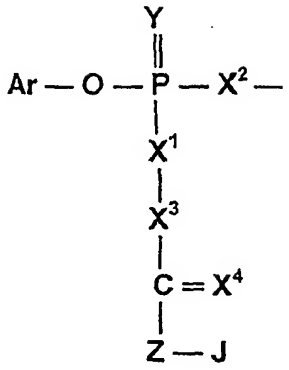


where R^9, R^{10}, R^{11}, R^{12} are independently selected from H, OH, N_3, halogen, CN, NH_2, CO-alkyl and alkyl.

Preferably, the masked phosphate moiety is



wherein Ar is an aryl group;

Y is oxygen or sulphur;

X^1 is selected from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

X^2 may be absent or selected (independently of X^1) from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

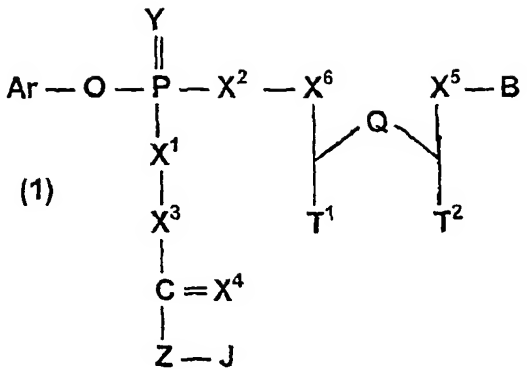
X^3 is a C_{1-6} alkyl group;

X^4 is oxygen or CH_2;

Z is selected from O, NR^5, S, alkyl and aryl groups, where R^5 is selected from hydrogen, alkyl and aryl groups;

J is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups.

According to another aspect of the invention there is provided a compound of the formula (1)



(1)

wherein Ar is an aryl group;

Y is oxygen or sulphur;

X^1 is selected from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

X^2-X^6 may be absent; or X^6 is CH_2 and X^2 is selected (independently of X^1) from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

X^3 is a C_{1-6} alkyl group;

X^4 is oxygen or CH_2;

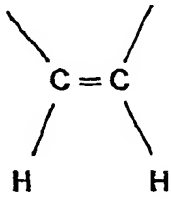
X^5 may be absent or is CH_2;

Z is selected from O, NR^5, S, alkyl and aryl groups, where R^5 is selected from hydrogen, alkyl and aryl groups;

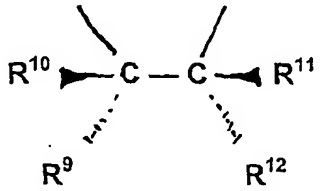
J is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups;

Q is selected from O, NR^6, S, CR^6R^7, CR^6W^3 and CW^3W^4, where R^6 and R^7 are independently selected from hydrogen, alkyl and aryl groups; and W^3 and W^4 are heteroatoms;

T^1 and T^2 are independently selected from hydrogen and CH_2R^8, where R^8 is selected from H, OH and F; or T^1 and T^2 are linked together and together are selected from the groups:

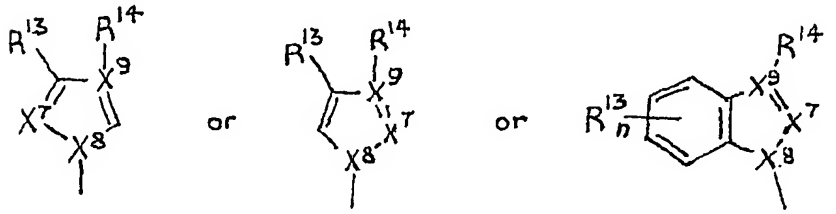


and



where R^9, R^{10}, R^{11}, R^{12} are independently selected from H, OH, N_3, halogen, CN, NH_2, CO-alkyl and alkyl;

wherein B is



wherein X^7, X^8 and X^9 are the same or different and each is C or N, when X^9 is N then there is no R^{14} group;

R^{13} and R^{14} are the same or different and each is H, NO_2, CO, COR^{15}, OR^{15}, CN, O, $CON(R^{15})_2$, $COOR^{15}$, SO_2R^{15}, SO_3R^{15}, SR^{15}, NHCHO, $(CH_2)_nN(R^{15})_2$ or halogen;

R^{15} is H or hydrocarbyl;

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable derivative or metabolite thereof.

Thus the compounds of the invention may contain modified pyrrole, indole, imidazole (including e.g. benzimidazole) or indazole units in place of the natural nucleic acid bases and it is a surprising feature of the invention that the masked (i.e. phosphoramidated) nucleoside

analogues containing these unusual bases (which in some cases are entirely devoid of biological activity) may exhibit selective antiviral activity at levels as low as 1μM.

Reference in the present specification to an alkyl group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5 to C_7.

Where acyclic, the alkyl group is preferably C_1 to C_{16}, more preferably C_1 to C_6, more preferably methyl. Reference in the present specification to alkoxy and aryloxy groups means alkyl-O- and aryl-O- groups, respectively. Reference to alkoyl and aryloyl groups means alkyl-CO- and aryl-CO-, respectively.

Reference in the present specification to an aryl group means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl and thiophenyl. Preferably, the aryl group comprises phenyl or substituted phenyl.

The alkyl and aryl groups may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, alkylamino, dialkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulphoxide; heterocyclic groups which may themselves be substituted; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl. Alkyl includes substituted and unsubstituted benzyl.

Reference in the present specification to heterocyclic groups means groups containing one or more, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

References in the present specification to polycyclic groups means a group comprising two or more non-aromatic carbcyclic or heterocyclic rings which may themselves be substituted.

Reference in the present specification to halogen means a fluorine, chlorine, bromine or iodine radical, preferably fluorine or chlorine radical.

The group Ar comprises a substituted or unsubstituted aryl group, wherein the term "aryl group" and the possible substitution of said group is as defined above. Preferably, Ar is a substituted or unsubstituted phenyl group. Particularly preferred substituents are electron withdrawing groups such as halogen (preferably chlorine or fluorine), trihalomethyl (preferably trifluoromethyl), cyano and nitro groups. Preferably, Ar is phenyl, 3,5-dichloro-phenyl, p-trifluoromethyl-phenyl, p-cyano-phenyl, or p-nitro-phenyl.

Y may be oxygen or sulphur. Preferably, Y is oxygen.

Preferably, X^1 is selected from O,S and NR^3. Preferably, X^1 is NR^3. When present, R^3 is preferably H. When present, W^1 and W^2 may independently comprise any heteroatom such as a halogen, preferably fluorine.

When present, X^2 is preferably oxygen. When present, R^3 is preferably H. When present W^1 and W^2 may independently comprise any heteroatom such as halogen, preferably fluorine.

Preferably, X^4 is oxygen.

Preferably, Z is O or NR^5. Preferably, R^5 is hydrogen. Most preferably, Z is oxygen.

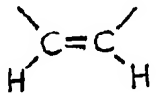
Preferably, J is a substituted or unsubstituted alkyl group. Preferably, J is a substituted or unsubstituted C_{1-6} alkyl group, preferably a benzyl or methyl group.

X^3 may be a C_{1-6} substituted or unsubstituted, branched or unbranched, methylene chain. Preferably, X^3 is a group CR^1R^2 where R^1 and R^2 are independently selected from hydrogen, alkyl and aryl groups. Preferably, at least one of R^1 and R^2 is hydrogen. It will be appreciated that if R^1 and R^2 are different, the carbon atom to which they are bonded is an asymmetric centre. The stereochemistry at this site may be R or S or mixed. When one of R^3 and R^4 is hydrogen, the stereochemistry is preferably S.

Where present in Q, W2 and W3 are preferably halogen atoms, preferably fluorine. Preferably, Q is O, S, CH_2 or CF_2. Most preferably, Q is oxygen.

When present in T^1 and T^2, R^9 is H or F and/or R^{10}, R^{11} and R^{12} are independently selected from H, F and N_3. It will be appreciated that R^9 corresponds to the 3' – α position and R^{10} corresponds to the 3' - ß position.

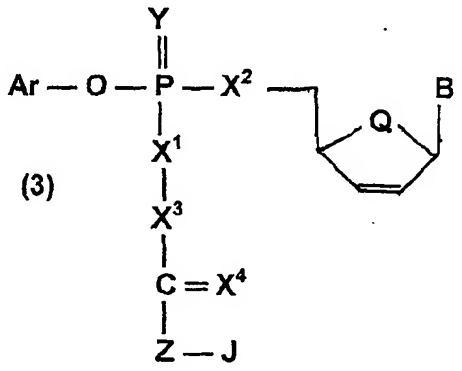
Preferably, T^1 and T^2 are linked together and together form the group:



Preferably, Y is oxygen, X^1 is NH, X^3 is CHR^1, X^4 is oxygen and Z is oxygen.

It will be appreciated that the group -NH- CHR^1-CO_2J corresponds to a carboxy-protected α-amino acid. Preferably, the group R^1 corresponds to the side chain of a naturally occurring amino acid such as Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine, Cystine, Glycine, Glutamic Acid, Glutamine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine. Preferably, R^1 is Me or $PhCH_2$ corresponding to the side chain of alanine or phenylalanine, respectively. Preferably, the stereochemistry at the asymmetric centre -CHR^1- corresponds to an L-amino acid.

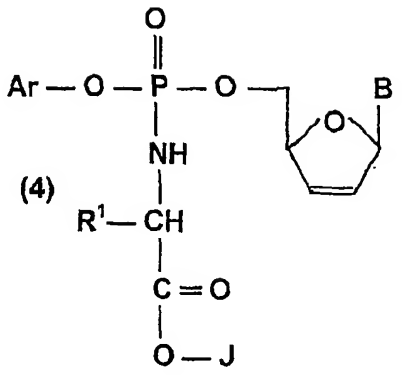
According to one preferred embodiment, the present invention provides a compound of formula (3):



(3)

wherein Ar, Y, X^1, X^2, X^3, X^4, Z, Q and B are as defined above.

More preferably, the invention provides a compound, according to formula (3), of formula (4):



(4)

wherein Ar, R^1 and J are as defined above; or a pharmaceutically acceptable derivative or metabolite thereof.

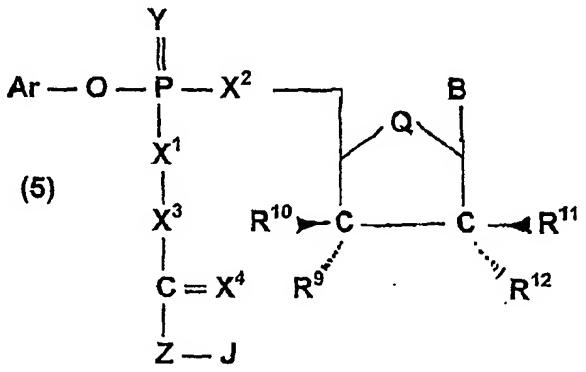
Preferably, the invention provides a compound of formula (4) in which Ar, R^1 and J are defined in accordance with Table 1.

Table 1

Ar	R^1	J
4-EtPh	Me	Me
Ph	Me	Me
4-FPh	Me	Me
3-CF_3Ph	Me	Me
3,5-Cl_2Ph	Me	Me
Ph	Me	Bzl
2,4-Br_2Ph	Me	Me
F_5Ph	Me	Me
Ph	Me	Hexyl
Ph	Bzl	Me
Ph	CH_2iPr	Me
Ph	iPr	Me
Ph	H	Me
Ph	$[CH_2]_2$ SMe	Me
2,4-Br_2Ph	Me	Bzl
Ph	Bzl	Bzl
Ph	Bzl	tBu
Ph	Me	Cyclohexyl
Ph	Me	tBu
Ph	CH_2 CO_2H	Me

Ph	$CH_2CH_2CH_2NHC[NH_2]NH$	Me
Ph	Me	n-Pent
Ph	Me	Neo-Pent
Ph	Me	1-Napthyl
Ph	Me	2-Napthyl

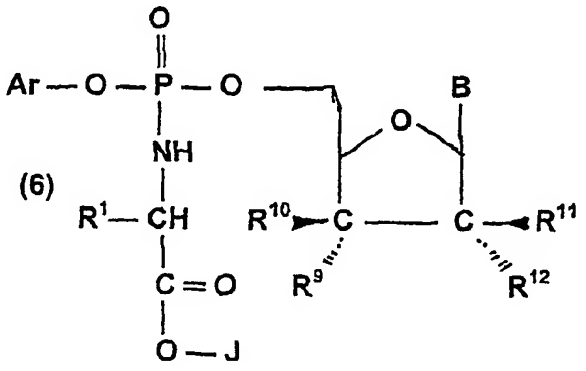
According to another preferred embodiment, the present invention provides a compound of formula (5)



(5)

wherein Ar, Y, X^1, X^2, X^3, X^4, Z, J, R^9, R^{10}, R^{11}, R^{12}, Q and B are as defined above.

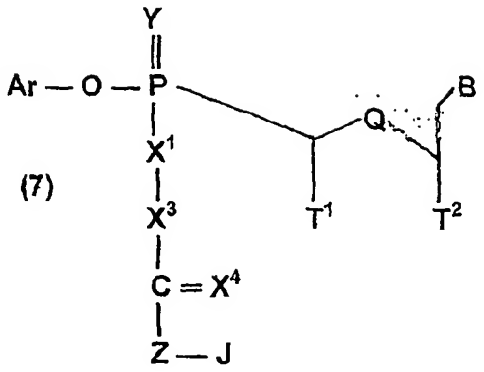
More preferably, the invention provides a compound, according to formula (5), of formula (6):



(6)

wherein Ar, R^1, J, R^9, R^{10}, R^{11}, R^{12} and B are as defined above.

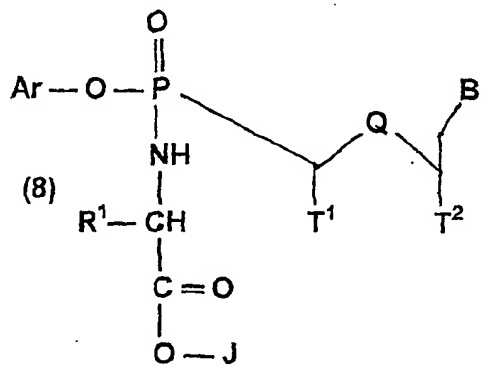
According to a further preferred embodiment, the present invention provides a compound of formula (7):



(7)

wherein Ar, Y, X^1, X^3, X^4, Z, J, Q and B are as defined above and T^1 and T^2 are independently selected from H and CH_2R^8 wherein R^8 is as defined above. Preferably, T^1 is hydrogen. Preferably, T^2 is CH_2R^8.

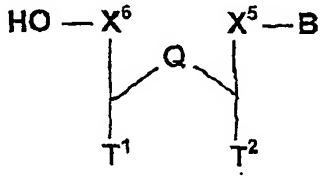
More preferably, the invention provides a compound, according to formula (7), of formula (8):



(8)

wherein Ar, R^1, J, T^1, T^2 and B are as defined above.

It is a feature of the compounds of the present invention that they exhibit significantly enhanced anti-viral efficacy, in both *in vitro* and *in vivo* tests, in comparison to their corresponding nucleoside analogue (9)



(9)

In addition, the compounds of the present invention exhibit significantly reduced toxicity in comparison to their corresponding analogue (9).

The compounds of the present invention thus exhibit a greatly enhanced selectivity index (ratio of CC (toxicity) : EC_{50} (activity)) in comparison to their corresponding nucleoside analogue.

The compounds of the present invention may also yield enhanced intracellular levels of nucleoside 5'-triphosphate, the enhancement being particularly significant in TX cells. Thus, the compounds of the present invention may act in part by the known metabolic pathway.

However, it has been found that the compounds of the present invention may also show surprising activity against nucleoside resistant strains of HIV. This indicates that the compounds of the present invention may also act by a pathway independent of a 5'-triphosphate metabolite.

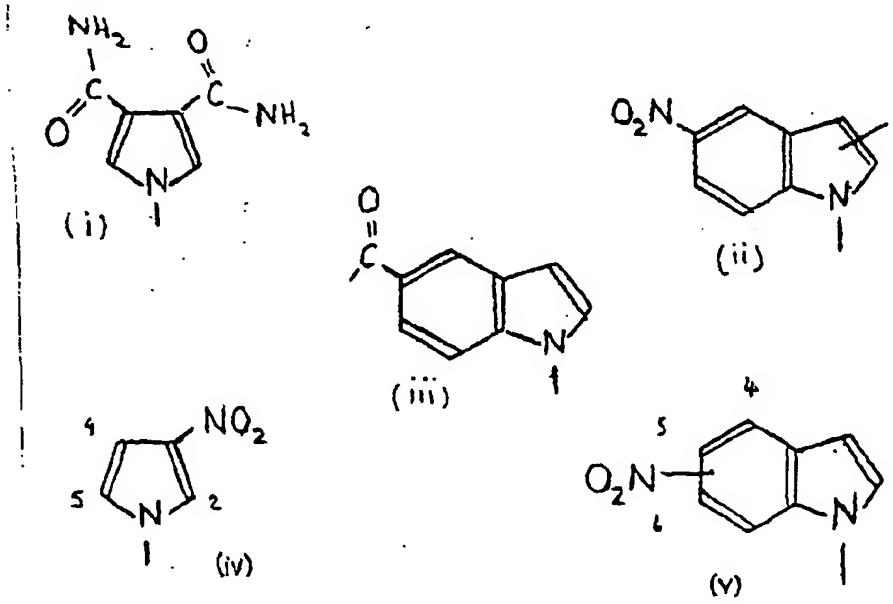
Preferably, in B

(a) X^7 and X^9 are C and X^8 is N; or

(b) R^{13} is H, X^8 and X^9 are N and X^7 is C; or

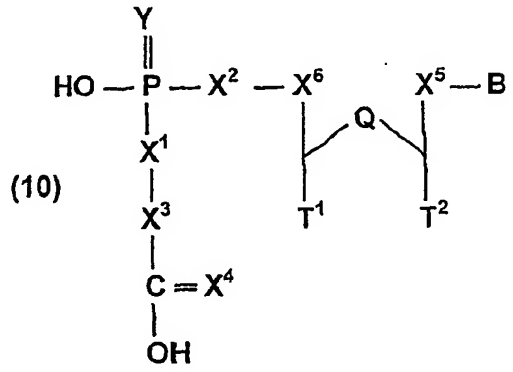
(c) R^{13} is H, R^{14} is NO_2, X^7 is C and X^8 is N.

Examples of preferred moieties B are:



Other examples of B are 3 -aminoethyl-5-nitroindole and 3-aminomethyl-4-carboxamido pyrrole.

The compounds of the invention described above lead to intracellular generation of high levels of a metabolite (10). Thus, according to another aspect of the invention there is provided a compound of formula (10)



(10)

wherein Ar, Y, X^1, X^2, X^3, X^4, X^5, T^1, T^2, Q and B are as defined above, or a pharmaceutically acceptable derivative or metabolite thereof.

Metabolite (10) may also be prepared by treatment of the corresponding compound according to formula (1) with hog liver esterase.

Compounds of formula (10) may be direct inhibitors of reverse transcriptase from HIV.

The intracellular generation of anti-viral metabolites such as (10) is an important feature of the invention for several reasons. Firstly, the direct activity of (10) on RT removes the necessity for further nucleotide-kinase mediated phosphorylation, which may be slow in many cases. In cases where the nucleoside monophosphate is not a substrate for host nucleotide kinases, activation will be poor and antiviral efficacy low, even if the triphosphate is an excellent RT inhibitor. In such cases, the generation of metabolites such as (10) may lead to a very significant enhancement in antiviral action. Such compounds may be acting directly in their own right or *via* a rearrangement, decomposition or disproportionation product or *via* a contaminant.

Moreover, the structure of metabolites such as (10) may be further designed to optimise binding to the known structure of RT, and such modified metabolites could be delivered intracellularly using technology herein described, to further enhance the anti-viral effect.

By "a pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, ester or salt of such ester or any other compound which upon administration to a recipient is

capable of providing (directly or indirectly) a compound of the invention (e.g. a compound of formula (1) or (10)).

By "pharmaceutically acceptable metabolite" is meant a metabolite or residue of a compound of the invention (e.g. a compound of formula (1) or (10)) which gives rise to a nucleoside-resistance independent or nucleoside 5'-triphosphate independent mode of reverse transcriptase inhibition exhibited by the compounds of the invention.

Medical applications

The compounds of the invention find application in medicine, for example in methods of therapy and/or prophylaxis.

Thus, according to a further aspect of the present invention the compound of the invention is provided in combination with a pharmaceutically acceptable excipient. Any suitable excipient may be used, including for example inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc.

In a further aspect, the invention provides a pharmaceutical composition comprising the compound of the invention. The pharmaceutical composition may take any suitable form, and includes for example tablets, elixirs, capsules, solutions, suspensions, powders, granules and aerosols. The pharmaceutical composition may take the form of a kit of parts, which kit may comprise the compound of the invention together with instructions for use. The pharmaceuticals of the invention may also comprise the compound of the invention in association (e.g. in admixture or co-packaged with) an adjunctive therapeutic. The adjunctive therapeutic may comprise an antiviral compound. In any of the foregoing pharmaceutical compositions, the compound of the invention may be present in unit dosage form.

In yet another aspect, there is provided a compound according to the invention for use in medicine, for example in therapy or prophylaxis.

According to a further aspect of the invention there is provided the use of a compound of the invention for the manufacture of a medicament for use in therapy or prophylaxis.

In a yet further aspect of the invention, there is provided a process for the manufacture of a medicament for use in therapy or prophylaxis characterized in the use of a compound of the invention (e.g. as an active ingredient).

In another aspect, the invention provides a method of therapy, prophylaxis or diagnosis comprising administration to a patient an effective dose of a compound according to the invention.

Preferably, the therapy or prophylaxis is the therapy or prophylaxis of a viral infection. The viral infection may comprise any viral infection such as herpes virus (including HSV 1 and HSV 2), CMV, VZV, EBV, HAV, HBV, HCV, HDV, papilloma, rabies and influenza.

In particularly preferred embodiments the viral infection is an HIV infection, including for example HIV-I or HIV-II: it is a feature of the present invention that the compounds exhibit good activity against both HIV-I and HIV-II. Thus, the invention finds application in the treatment or prevention of AIDS.

Without wishing to be bound by any theory, it is thought that the medical applications of the present invention rest on the ability of the compounds of the invention to inhibit reverse transcriptase. In particular, the compounds of the invention appear to inhibit reverse transcriptase in a nucleoside-resistance independent or nucleoside 5'-triphosphate independent manner.

Thus, according to a further aspect of the present invention there is provided use of a compound of the present invention in the manufacture of a medicament for use in the inhibition of a reverse transcriptase by a nucleoside-resistance independent or nucleoside 5'-triphosphate independent mode of action.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

According to a further aspect of the present invention there is provided a method of preparing a pharmaceutical composition comprising the step of continuing a compound of of the present invention with a pharmaceutically acceptable excipient.

The medicaments employed in the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

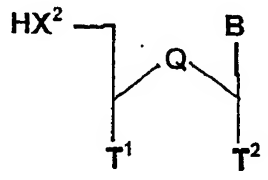
For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity.

Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

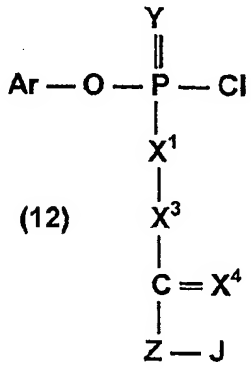
The compounds of the invention may also be presented as liposome formulations.

In general a suitable dose will be in the range of 0.1 to 300 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 150 mg per kilogram body weight per day and most preferably in the range 15 to 100 mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

According to a further aspect of the present invention there is provided a process for the preparation of a compound according to the present invention, the process comprising reaction of a compound of formula (11)

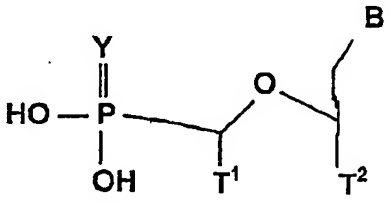
(11) 

with a compound of formula (12)

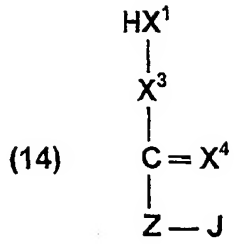
(12) 

The reaction may be carried out in the tetrahydrofuran in the presence of N-methylimidazole.

Alternatively, the compounds of the present invention may be prepared by reaction of a compound of formula (13) or a suitable derivative thereof

(13) 

with ArOH and a compound of formula (14) or suitable derivatives thereof



(14)

The invention will now be described with reference to the following exemplary embodiments, which are purely illustrative and not intended to be limiting in any way. It will be appreciated that modifications to detail may be made whilst still falling within the scope of the invention.

Examplification

The synthetic strategy used for the preparation of the aryloxy phosphoramidates closely follows published procedures (McGuigan, C., Pathirana, R.N., Mahmood, N., Devine, K.G. and Hay, A.J. (1992) Aryl phosphate derivatives of AZT retain activity against HIV1 in cell lines which are resistant to the action of AZT. Antiviral Res. 17, 311-321; McGuigan, C., Pathirana, R.N., Balzarini, J., and De Clercq, E. (1993) Intracellular delivery of bio-active AZT nucleotides by aryl phosphate derivatives of AZT. J. Med. Chem. 36, 1048-1052).

The procedure involves the initial preparation of the appropriate phosphorochloridate from phenyl phosphorodichloridate and an amine, followed by its reaction with the parent nucleoside analogue. Thus, reaction of the phenyl methylalaninyl phosphorochloridate with pyrrole nucleoside analogue (Loakes, D. and Brown, D.M. (1994) 5-Nitroindole as a universal base analogue. Nucleic Acids Res. 22, 4039-4043) in THF containing N-methylimidazole gave [2] in moderate yield after purification by column chromatography. This was isolated as a mixture of diastereoisomers, as evidenced by the presence of two closely spaced signals in the P-31 NMR [δ_P ca. 4 ppm] - this arising from mixed stereochemistry at the phosphorus centre. The presence of these isomers was further confirmed in the H-1 NMR spectrum, where the signal due to the carboxyl-methyl group showed extra multiplicity. Carbon-13 NMR data also confirmed the structure, purity, and isomeric nature of [2].

The synthetic route to [2] is shown in Scheme 2.

Similarly prepared and derivatised was the benzimidazole nucleoside [3] and its phosphoramidate [4], which is shown in Scheme 1.

All spectroscopic data fully confirmed the structure and purity of these materials, in each case again being isolated as mixtures of diastereoisomers about the phosphorus centre. All samples were pure by HPLC, and entirely free of any contaminating nucleoside.

The antiviral activities of compounds [1] - [4] were evaluated in MT4 and C8166 T-cell lines infected with HIV-1RF using the MTT cell viability assay or P24 reduction assay (Tables 2 and 3).

Table 2: anti HIV-1 activity and cytotoxicity of indole and pyrrole nucleosides and nucleotides in MT-4 cells using MTT cell viability assay

Compound	Cf	5'-group	Base Unit	EC_{50}	CC_{50}
1	1073	OH	3'-NO_2 pyrrole	>100 µM	>100 µM
2	1105	phosphoramidate	3'-NO_2 pyrrole	7.3 µM ± 2.8 µM	112 µM
3	1201	OH	Bzlm	>100 µM	41.0 µM ± 13.6 µM
4	1210	phosphoramidate	Bzlm	6.5 µM ± 2.8 µM	60.5 µM ± 6.6 µM

In Table 2, the data show the 50% effective dose (EC_{50}) and 50% cytotoxic dose (CC_{50}) for the nucleosides and nucleotides 1-4 for HIV-1_{RF} in MT-4 cells using the MTT cell viability assay.

Table 3: anti HIV-1 activity of indole and pyrrole nucleosides and nucleotides in C8166 T-cells using p24 reduction assay

Compound	Cf	5'-group	Base Unit	EC_{50}
1	1073	OH	3'-NO_2 pyrrole	>100 µM
2	1105	phosphoramidate	3'-NO_2 pyrrole	1.5 µM
3	1201	OH	Bzlm	>30 µM
4	1210	phosphoramidate	Bzlm	1.0 µM

In Table 3, the data show the 50% effective dose (EC_{50}) for the nucleosides and nucleotides 1-4 for HIV-1_{RF} in C8166 T-cells using a p24 reduction assay.

The parent nucleoside analogues [1] and [3] were noted to be non-active against HIV-1 at the concentrations tested , with EC_{50} values of >100µM.

On the other hand, it is notable that the phosphoramidates are active at µM concentrations. The methylalaninyl phosphoramidate derivative of 3-nitropyrrole [2] showed activity with an EC_{50} of 7.3 µM ± 2.8 µM and a CC_{50} of 112 µM; giving it a selectivity index (SI) of 15.3 in MT-

4 cells using a cell viability assay. In C8166 T-cells using a p24 reduction assay, this compound gave an EC_{50} of 1.5 μM.

The benzimidazole phosphoramidate [4] showed similar activity,with an EC_{60} of 6.5 μM ±2.8 μM and a CC_{50} of 60.5 μM ±6.6 μM in the MT-4 cell viability assay. The compound had an EC_{50} of 1.0 μM in C8166 T-cells using the p24 reduction assay. Thus, both phosphoramidates are considerably more potent than their parent nucleoside analogues [**1, 3**].

Thus, in conclusion the phosphoramidate derivatives of the invention are selective inhibitors of the proliferation of HIV-1 in tissue culture, whilst the parent nucleoside analogues are poorly active. This represents a further example of "kinase by-pass"; the activation of an inactive nucleoside analogue by virtue of judicious chemical phosphorylation leading to the intracellular delivery of free nucleotides and a by-pass of the dependence on nucleoside kinase-mediated activation.

Experimental methods

All experiments involving water-sensitive compounds were conducted under scrupulously dry conditions. Tetrahydrofuran was dried by heating under reflux over sodium and benzophenone followed by distillation. N-methylimidazole was purified by distillation. Nucleosides were dried by storage at elevated temperature *in vacuo* over P_2O_5. Proton, carbon and phosphorus Nuclear Magnetic Resonance (^1H, ^{13}C, ^{31}P NMR) spectra were recorded on a Bruker Avance DPX spectrometer operating at 300MHz, 75.5MHz, and 121.5MHz respectively. All NMR spectra were recorded in $CDCl_3$ at room temperature (20°C ±3°C). ^1H and ^{13}C chemical shifts are quoted in parts per million downfield from tetramethylsilane.

J values refer to coupling constants and signal splitting patterns are described as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), multiplet (m) or combinations thereof. ^{31}P chemical shifts are quoted in parts per million relative to an external phosphoric acid standard. Many proton- and carbon-NMR signals were split due to the presence of [phosphate] diastereoisomers in the samples.

The mode of ionisation for mass spectroscopy unless stated was fast atom bombardment (FAB) with MNOBA as matrix. Chromatography refers to flash column chromatography and was carried out using Merck silica gel 60 (40-60 μM) as stationary phase. Thin layer chromatography was performed using Alugram SIL G/UV_{254} aluminium backed silica gel plates. HPLC was conducted on an ACS quaternary system, using an ODS5 column and an eluant of water/acetonitrile, with 82% water 0-10 min, then a linear gradient to 20% water at 30 min, with a flow rate of 1 ml/min and detection by UV at 265 nm.

General procedure for the preparation of phenyl phosphoramidates of nucleoside analogues

In a round-bottomed flask provided with a magnetic stirrer and nitrogen inlet the appropriate nucleoside analogue (0.30 mmol) and N-methylimidazole (0.9 mmol) were dissolved in THF (ca. 3 ml). To this the appropriate phenyl N-alkyl phosphoryl chloride (0.36 mmol) dissolved in THF (1 ml) was added dropwise with a syringe over 5 minutes and the reaction mixture was left stirring for 14 h at ambient temperature. The mixture was dissolved in chloroform (50 ml) and washed with 1M HCl (20 ml), saturated $NaHCO_3$ (20 ml), water (20 ml), dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was purified by column chromatography on silica using $CHCl_3$-MeOH 50:1 as eluant. The title compounds were obtained as colourless oils.

1-[ß-(3-nitropyrrole-1-yl)]-5-[(N-(methylalaninyl))(phenyl)phosphoryl]-2-deoxy-D-ribose [2]

Yield: 15.5% δ_H ($CDCl_3$) 1.39 (d, J = 7.0 Hz, 3H, Ala-Me), 2.25-2.60 (m, 2H, H2'), 3.73, 3.75 (2 x s, 3H, CO2CH3), 4.05-4.56 (m, 6H, H3', H4', H5', Ala-CH, Ala-NH), 5.90 (m, 1H, H1'), 6.70 (dd, J = 2.2 , 2.7 Hz, 1H, pyrrole), 6.77 (dd, J = 1.9 , 2.7 Hz, 1H, pyrrole), 7.20-7.42 (m, 5H, Ph), 7.75, 7.79 (2 x dd, J = 1.9, 2.2 Hz, 1H, pyrrole); δ_C ($CDCl_3$) 20.64, 20.71 (Ala-Me), 41.07, 41.15 (C2'), 50.15, 50.23 (Ala-CH), 52.60, 52.66 (CO_2CH_3), 65.53, 65.59, 65.86, 65.94 (2 x d, C5'), 70.27, 70.54 (C3'), 84.85, 84.94, 85.15, 85.24 (2 x d, C4'), 88.11, 88.36 (C1'), 105.90-120.05 (pyrrole), 125.24-129.84 (Ph), 137.42 (pyrrole), 150.34, 150.43 (Ph-ipso), 173.84, 173.89, 174.9 (C=O); δ_P ($CDCl_3$) 4.21, 4.57 (2:3); FAB MS m/e 470.1328 (MH^+, $C_{19}H_{25}N_3O_9P$ requires 470.1328, 14%); HPLC (RT) 27.17 min.

General procedure for glycosidation via a furanoid glycal intermediate

To a stirred mixture of the corresponding heterocyclic base (1.39 mmol) in dry CH_2Cl_2 (10 mL) 2 eq of *N,O*-bis (trimethylsilyl)acetamide (2.78 mmol) were added and the mixture was heated to reflux until the solution became clear (30 – 60 min). After allowing to cool to room temperature a solution of the furanoid glycal SV-2b-6 (0.20g, 1.16 mmol) in CH_2Cl_2 (2mL) and approximately 300 mg of 4Å powdered molecular sieves were added to the previous sylilated base solution. The resulting mixture was stirred for 15 min at room temperature, cooled to -20°C and then N-iodosuccinimide (0.313 g, 1.39 mmol) was added. After being stirred for 1h, the mixture was filtered and ethyl acetate (50 mL) and 10% aqueous $Na_2S_2O_3$ (50 mL) were added. The organic phase was removed and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organics were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (hex/ethyl acetate, 1:1) to give the corresponding 2'-iodonucleosides.

1-(2',3'-dideoxy-2'-iodo-5'-O-(pivaloyl)-ß-D-ribofuranosyl) benzimidazole

Following the general procedure benzimidazole (0.165g, 1.39 mmol) was silylated with *N,O*-bis (trimethylsilyl)acetamide (0.69 mL, 2.78 mmol) for 30 min and then reacted with the glycal (0.20g, 1.16 mmol) and N-iodosuccinimide (0.313 g, 1.39 mmol) for 1h. The residue, a

mixture 10/1 of the b/a anomers (determined by ^{1}HNMR of the crude), was purified by column chromatography (hex/ethyl acetate, 1:1). The fastest moving band gave the b-isomer (SV-2b-36a) as a yellow foam (0.225g, 51%).

^{1}HNMR ($CDCl_3$) 8.20 (1H, s, H-2), 7.89-7.33 (4H, m, aromatics), 6.46 (1H, d, H-1', J1',2'=3.4 Hz), 4.82 (1H, m, H-4'), 4.41-4.60 (3H, m, H-2', 2H-5'); 2.49 (2H, m, 2H-3'), 1.28 (9H, s, 3CH3) MS (ES+) 451 (M+Na, base)

1-(2',3'-dideoxy-b-D-glycero-pent-2-enofuranosyl)-benzimidazole Cf1201 [3]

The iodonucleoside (0.150g, 0.36mmol) was treated with a freshly prepared solution of MeONa in MeOH (10.8 mmol=0.25g Na in 10 mL MeOH) at room temperature for 6h. The reaction mixture was carefully neutralized with HCl1N-MeOH and concentrated to dryness. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 10:1) to afford (SV-2b-37) (0.058g, 92%) as a white foam.

^{1}HNMR ($CDCl_3$) 8.01 (1H, s, H-2), 7.58-7.08 (4H, m, aromatics), 6.80 (1H, m, H-1'), 4.42 (1H, m, H-3'), 6.01 (1H, m, H-2'), 5.00 (1H, m, H-4'), 3.86 (1H, m, H-5', J4',5'=3.1, J5',5'=12.5 Hz), 3.70 (1H, m, H-5', J4',5'=3.6 Hz).

^{13}CNMR ($CDCl_3$) 142.92, 132.98 (C-4,C-5), 141.54 (C-2), 134.98 (C-3'), 125.09 (C-2'), 123.14, 122.41, 119.98, 109.78 (aromatics), 89.29, 88.36 (C-1', C-4'), 63.02 (C-5').

MS(ES+) 239 (M+Na, base). $C_{12}H_{12}N_2$

HPLC RT 12.71 (acetonitrile/water, 55/45)

1-(2',3'-dideoxy-5'-(phenylmethoxyalaninylphosphate)-ß-D-glycero-pent-2-enofuranosyl) benzimidazol Cf1210 [4]

Phenyl methoxyalaninyl phosphorochloridate (0.574 mmoles, 2.0 equiv) was added to a stirred solution of [3] (0.05g, 0.287 mmoles) and N-methylimidazole (137 µl, 1.72 mmoles, 6 equiv) in dry THF (2 mL) at ambient temperature. After 3 h water was added and the solvent removed under pressure. The residue was dissolved in $CHCl_3$ (10 mL), washed with 1NHCl (10 mL), water (10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by chromatotron (CH_2Cl_2/MeOH, 20:1) to give SV2b63 (66 mg, 56%) as a white foam.

^{31}PNMR 4.52, 4.27 (1:1)

^{1}HNMR ($CDCl_3$) 8.50, 8.30 (1H, s, H-2), 7.95-6.98 (10H, m, Aromatics, H-1'), 6.55, 6.43 (1H, m, H-3'), 6.25, 6.19 (1H, m, H-2'), 5.15 (1H, m, H-4'), 4.24 (2H, m, 2H-5'), 4.06 (1H, m, Ala-CH), 3.76 (1H, m, Ala-NH), 3.62,3.65 (3H, s, Ala-OCH3), 1.02, 1.35 (3H, d, Ala-CH3, J=7.0 Hz).

^{13}CNMR ($CDCl_3$) 173.83, 173.74 (CO2Me), 150.53, 150.45, 150.36 (Phipso-POPh), 141.22, 141.05, 132.63, 124,09, 123.83, 123.58, 119.68, 119.46, 110.57, 110.41 (Aromatics-Bzi), 134.31, 133.99 (C-3'), 129.63, 129.55 (Phmeta-POPh), 125.80, 125.77 (C-2'), 124.87, 124.30 (Phpara-OPh), 120.30, 120.22, 120.16 (d, Phorto-POPh, $J_{P,C}$=5.5, 5.1 Hz), 89.91, 89.80 (C-1'), 85.84, 85.79, 85.73, 85.67 (d, C-4', $J_{P,C}$=4.2, 4.4 Hz), 66.90, 66.83, 66.34, 66.28 (d, C-5',

$J_{P,C}$=5.5, 4.5 Hz), 52.39, 52.33 (Ala-OCH3), 50.30, 49.98 (Ala-CH), 20.59, 20.53, 20.30, 20.23 (d, Ala-CH3, $J_{P,C}$=4.4, 5.1 Hz).
MS(ES+) 480 (M+Na, base) $C_{22}H_{24}N_3O_6P$ requires 457.426
HPLC RT 26.03, 26.45

Antiviral Assays

The anti-HIV-1 activities and toxicities of compounds were assessed in MT-4 cells using the MTT cell viability assay as previously described (Pauwels, R., Balzarini, J., Schols, D., Baba, M., Desmyter, J., Rosenberg, I., Holy, A., and De Clercq, E. (1988) Rapid and automated tetrazolium-based colorimetric assay for the detection of anti-HIV compounds. J. Virol. Methods, 20, 309-321).

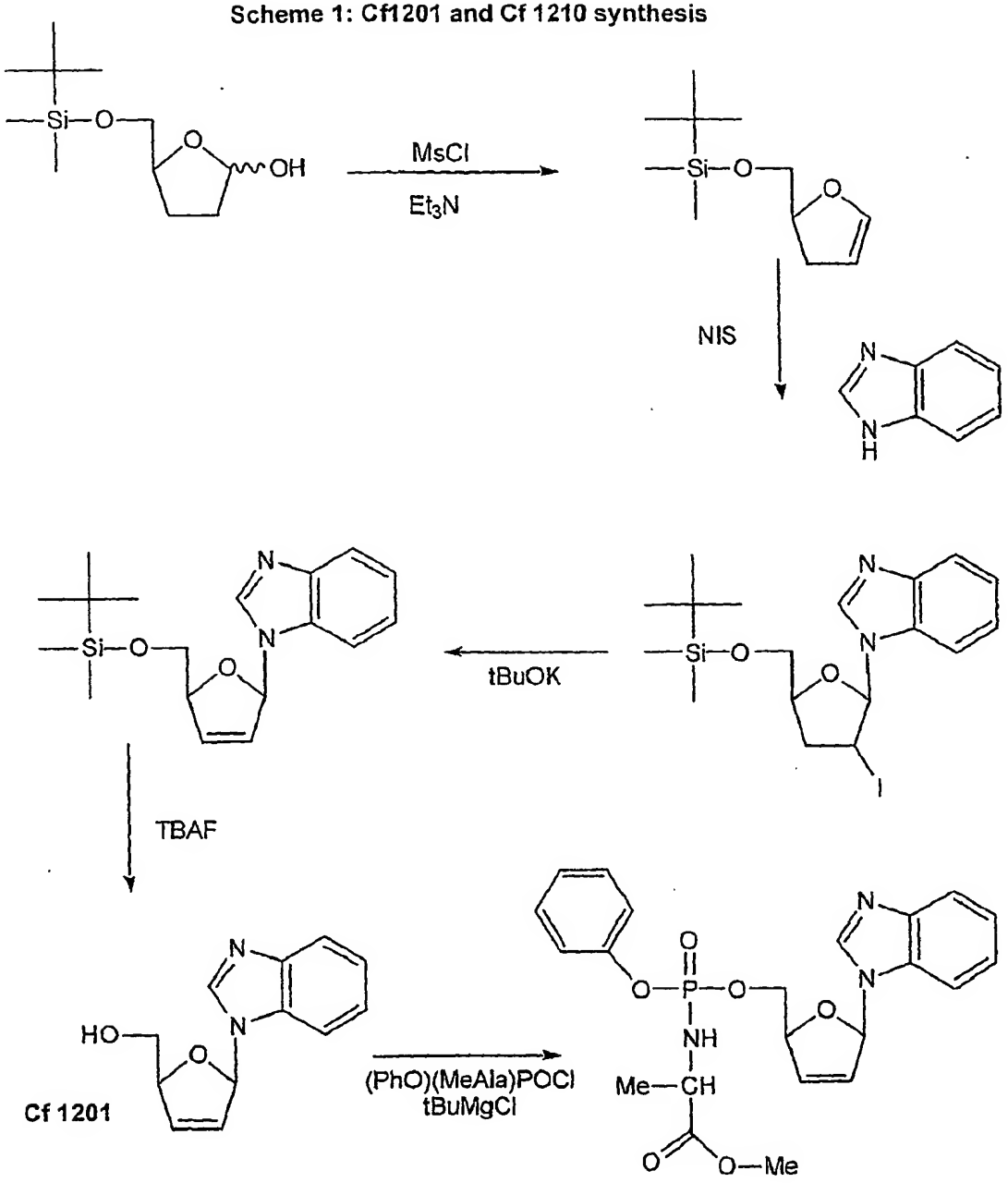
Briefly, MT-4 cells were infected for 1h at room temperature at low multiplicity. The cells were then washed and distributed into triplicate wells of 96-well cell culture plates, containing different concentrations of test compounds, or no compound, at a concentration of 5 x 104 cells per well. The plates were incubated at 37°C for 6 days and then cell viability was assessed by adding 10 µl of MTT (7.5 mg/ml) in PBS to each well, and then incubating the plates for an additional hour. The formazan crystals which formed were solubilised by adding 100 µl of acidified isopropanol to each well and mixing. The absorbance was read at 540 nm, and dose-response curves of OD versus drug concentration were plotted. Cytotoxicity was assesssed in parallel by culturing uninfected cells in the same concentrations as test compounds.

Anti-HIV activity was confirmed in C8166 T-cells infected with HIV-1RF using a p24 reduction assay. Briefly, C8166 cells were infected with HIV-1RF at low multiplicity for 2h at room temperature. The cells were then washed 3 times, distributed into wells of 48-well cell culture plates containing different concentrations of test compound, or no compound, and incubated at 37°C. After 3 days, the cell-free culture fluid was harvested and assayed for levels of viral p24 antigen using a commercially available ELISA (Murex), according to the manufacturer's instructions. Dose-reponse curves were plotted of p24 (% inhibition compared with untreated controls) versus drug concentration.

Equivalents

The foregoing descriptions detail presently preferred embodiments of the present invention. Numerous modifications and variations in practice thereof are expected to occur to those skilled in the art upon consideration of these descriptions. Those modifications and variations are intended to be encompassed within the claims appended hereto.

Scheme 1: Cf1201 and Cf 1210 synthesis



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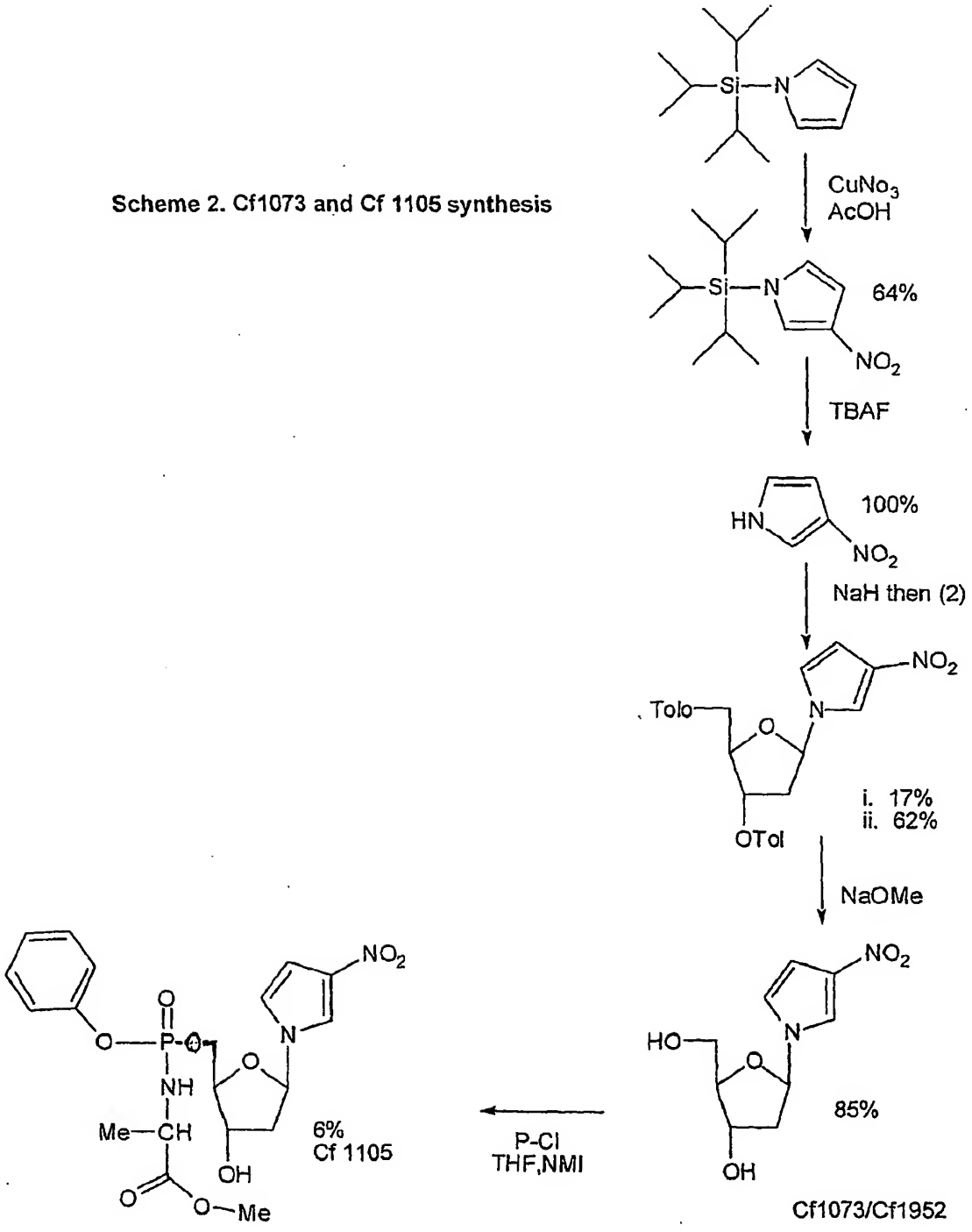
Scheme 2. Cf1073 and Cf 1105 synthesis

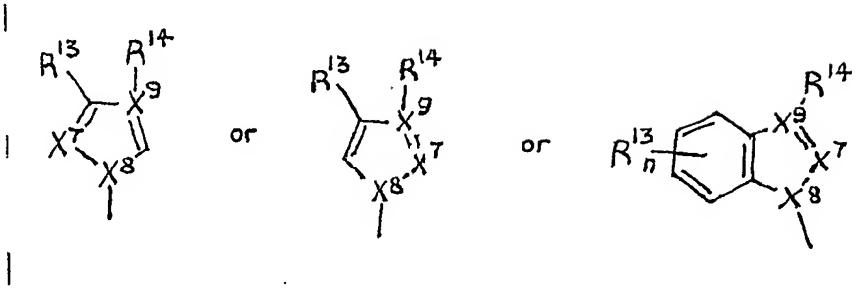


CLAIMS:

1. A compound of general formula:

[masked phosphate] - [sugar] - B

wherein B is



wherein X^7, X^8 and X^9 are the same or different and each is C or N, when X^9 is N then there is no R^{14} group;

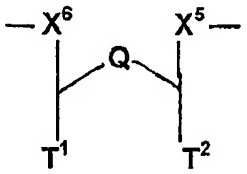
R^{13} and R^{14} are the same or different and each is H, NO_2, CO, COR^{15}, OR^{15}, CN, O, $CON(R^{15})_2$, $COOR^{15}$, SO_2R^{15}, SO_3R^{15}, SR^{15}, NHCHO, $(CH_2)_nN(R^{15})_2$ or halogen;

R^{15} is H or hydrocarbyl;

n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable derivative or metabolite thereof.

2. A compound according to claim 1 wherein the sugar moiety is



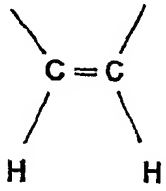
wherein

X^6 may be absent or is CH_2;

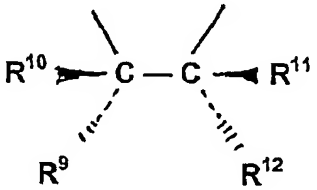
X^5 may be absent or is CH_2;

Q is selected from O, NR^6, S, CR^6R^7, CR^6W^3 and CW^3W^4 , where R^6 and R^7 are independently selected from hydrogen, alkyl and aryl groups; and W^3 and W^4 are heteroatoms;

T^1 and T^2 are independently selected from hydrogen and CH_2R^8, where R^8 is selected from H, OH and F; or T^1 and T^2 are linked together and together are selected from the groups:

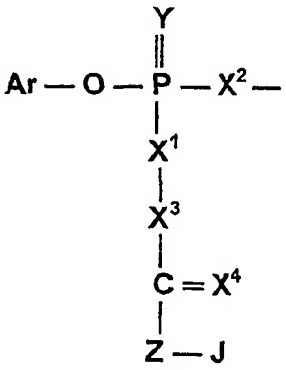


and



where R^9, R^{10}, R^{11}, R^{12} are independently selected from H, OH, N_3, halogen, CN, NH_2, CO-alkyl and alkyl.

3. A compound according to claim 1 or claim 2 wherein the masked phosphate moiety is



wherein Ar is an aryl group;

Y is oxygen or sulphur;

X^1 is selected from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

X^2 may be absent or selected (Independently of X^1) from O, NR^3, S, CR^3R^4,

CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

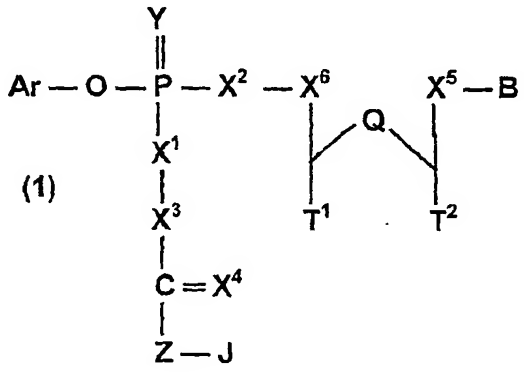
X^3 is a C_{1-6} alkyl group;

X^4 is oxygen or CH_2;

Z is selected from O, NR^5, S, alkyl and aryl groups, where R^5 is selected from hydrogen, alkyl and aryl groups;

J is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups.

4. A compound of the formula (1)



(1)

wherein Ar is an aryl group;

Y is oxygen or sulphur;

X^1 is selected from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

X^2-X^6 may be absent; or X^6 is CH_2 and X^2 is selected (independently of X^1) from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

X^3 is a C_{1-6} alkyl group;

X^4 is oxygen or CH_2;

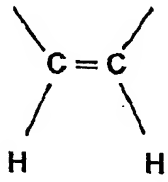
X^5 may be absent or is CH_2;

Z is selected from O, NR^5, S, alkyl and aryl groups, where R^5 is selected from hydrogen, alkyl and aryl groups;

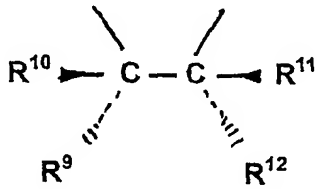
J is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups;

Q is selected from O, NR^6, S, CR^6R^7, CR^6W^3 and CW^3W^4 , where R^6 and R^7 are independently selected from hydrogen, alkyl and aryl groups; and W^3 and W^4 are heteroatoms;

T^1 and T^2 are independently selected from hydrogen and CH_2R^8, where R^8 is selected from H, OH and F; or T^1 and T^2 are linked together and together are selected from the groups:

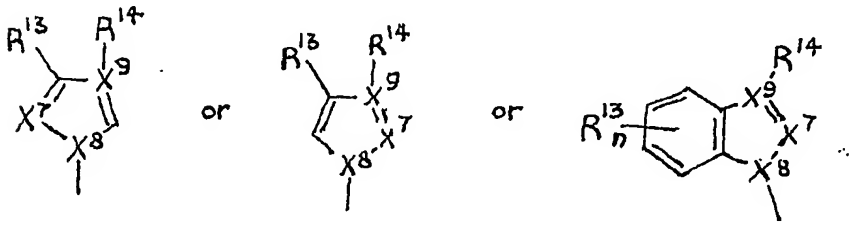


and



where R^9, R^{10}, R^{11}, R^{12} are independently selected from H, OH, N_3, halogen, CN, NH_2, CO-alkyl and alkyl;

wherein B is



wherein X^7, X^8 and X^9 are the same or different and each is C or N, when X^9 is N then there is no R^{14} group;

R^{13} and R^{14} are the same or different and each is H, NO_2, CO, COR^{15}, OR^{15}, CN, O, $CON(R^{15})_2$, $COOR^{15}$, SO_2R^{15}, SO_3R^{15}, SR^{15}, NHCHO, $(CH_2)_nN(R^{15})_2$ or halogen;

R^{15} is H or hydrocarbyl;

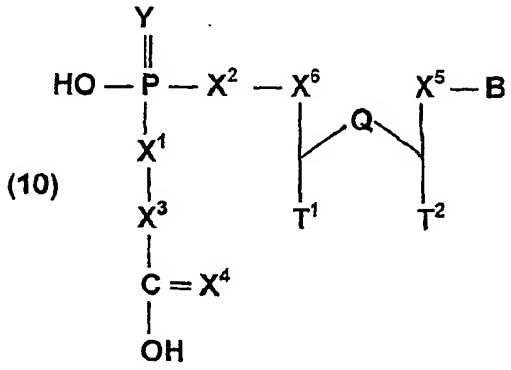
n is 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable derivative or metabolite thereof.

5. A compound according to claim 4 wherein

Y is oxygen;
X^1 is NH;
X^3 is CHR^1;
X^4 is oxygen; and
Z is oxygen.

6. A compound of formula (10)



(10)

wherein Y is oxygen or sulphur;

X^1 is selected from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

X^2-X^6 may be absent; or X^6 is CH_2 and X^2 is selected (independently of X^1) from O, NR^3, S, CR^3R^4, CR^3W^1 and CW^1W^2 where R^3 and R^4 are

independently selected from hydrogen, alkyl and aryl groups; and W^1 and W^2 are heteroatoms;

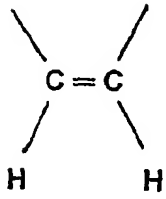
X^3 is a C_{1-6} alkyl group;

X^4 is oxygen or CH_2;

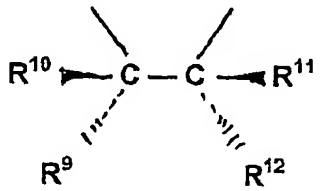
X^5 may be absent or is CH_2;

Q is selected from O, NR^6, S, CR^6R^7, CR^6W^3 and CW^3W^4 , where R^6 and R^7 are independently selected from hydrogen, alkyl and aryl groups; and W^3 and W^4 are heteroatoms;

T^1 and T^2 are independently selected from hydrogen and CH_2R^8, where R^8 is selected from H, OH and F; or T^1 and T^2 are linked together and together are selected from the groups:

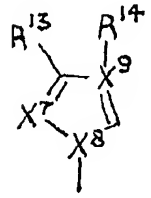


and

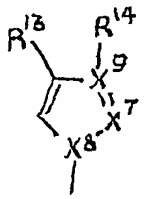


where R^9, R^{10}, R^{11}, R^{12} are independently selected from H, OH, N_3, halogen, CN, NH_2, CO-alkyl and alkyl;

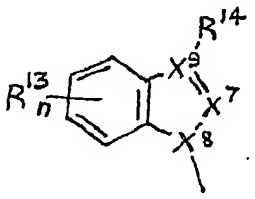
wherein B is



or



or



wherein X^7, X^8 and X^9 are the same or different and each is C or N, when X^9 is N then there is no R^{14} group;

R^{13} and R^{14} are the same or different and each is H, NO_2, CO, COR^{15}, OR^{15}, CN, O, $CON(R^{15})_2$, $COOR^{15}$, SO_2R^{15}, SO_3R^{15}, SR^{15}, NHCHO, $(CH_2)_nN(R^{15})_2$ or halogen;

R^{15} is H or hydrocarbyl;

n is 0, 1, 2, 3 or 4;

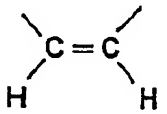
or a pharmaceutically acceptable derivative or metabolite thereof.

7. A compound according to claim 6 wherein

Y is oxygen;
X^1 is NH;
X^3 is CHR^1; and
X^4 is oxygen.

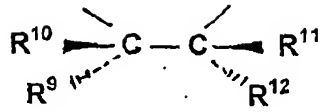
8. A compound of any one of claims 4 to 7 wherein

X^2 is oxygen;
X^6 is CH_2;
Q is oxygen;
X^5 is absent; and
T^1 and T^2 together comprise the group:



9. A compound of any one of claims 4 to 7 wherein

X^2 is oxygen;
X^6 is CH_2;
Q is oxygen;
X^5 is absent; and
T^1 and T^2 together comprise the group:



10. A compound of any one of claims 4 to 7 wherein

X^2- X^6 is absent;
Q is oxygen;
X^5 is CH_2;
T^1 and T^2 are independently selected from hydrogen and CH_2R^8 wherein R^8 is selected from H, OH and F.

11. A compound according to any one of the preceding claims wherein in B

(d) X^7 and X^9 are C and X^8 is N; or
(e) R^{13} is H, X^8 and X^9 are N and X^7 is C; or
(f) R^{13} is H, R^{14} is NO_2, X^7 is C and X^8 is N.

12. The compound of any one of the preceding claims in combination with a pharmaceutically acceptable excipient.

13. A pharmaceutical composition comprising the compound of any one of claims 1 to 11.

14. A compound of any one of claims 1 to 11 for use in therapy or prophylaxis.

15. Use of the compound of any one of claims 1 to 11 for the manufacture of a medicament for use in therapy or prophylaxis.

16. A process for the manufacture of a medicament for use in therapy or prophylaxis characterized in the use of a compound as defined in any one of claims 1 to 11.

17. A method of therapy or prophylaxis comprising administration to a patient in need thereof an effective dose of a compound according to any one of claims 1 to 12 or composition of claim 13.

18. The compound of claim 14, use of claim 15, process of claim 16 or method of claim 17 wherein the therapy or prophylaxis is the therapy or prophylaxis of a viral infection.

19. The compound, use, process or method of claim 18 wherein the viral infection is HIV infection.

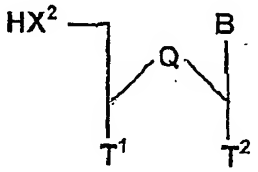
20. The compound, use, process or method of claim 19 wherein the therapy or prophylaxis is the treatment or prevention of AIDS.

21. The compound, use, process or method of any one of claims 18 to 20 wherein the therapy or prophylaxis comprises the inhibition of a reverse transcriptase.

22. The compound, use, process or method of claim 21 wherein the inhibition of reverse transcriptase is nucleoside-resistance independent or nucleoside 5'-triphosphate independent.

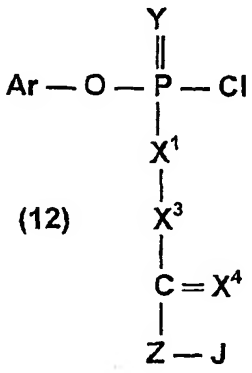
23. A process for the preparation of a compound according to any one of claims 1 to 11 comprising reaction of a compound of formula (11)

(11)



with a compound of formula (12)

(12)



24. The compound, use, process or method of any one of the preceding claims wherein the compound is selected from:

(a) 1-(2',3'-dideoxy-5'-(phenylmethoxyalaninylphosphate)-ß-D-glycero-pent-2-enofuranosyl) benzimidazol (Cf1210); and

(b) 1-[ß-(3-nitropyrrole-1-yl)]-5-[(N-(methylalaninyl))(phenyl)phosphoryl]-2-deoxy-D-ribose (Cf1105).

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/04 C07H19/044 C07H19/052 C07H19/056 A61K31/7056 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 29336 A (MEDICAL RES COUNCIL ;UNIV CARDIFF (GB); REGA FOUNDATION (BE); MCGU) 26 September 1996 (1996-09-26) the whole document ---	1-23
Y	WITKOWSKI J T ET AL: "Design, synthesis, and broad spectrum antiviral activity of 1-beta-D-ribofuranosyl-1,2,3-triazole-3-carboxamide and related nucleosides" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 15, 1972, pages 1150-1154, XP002164810 ISSN: 0022-2623 the whole document --- -/--	1-23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 April 2003	23/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax (+31–70) 340–3016	de Nooy, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 309 969 A (AMERSHAM INT PLC) 13 August 1997 (1997-08-13) the whole document ---	1
A	WO 00 47591 A (GLAXO GROUP LTD ;UNIV CARDIFF (GB); MCGUIGAN CHRISTOPHER (GB); DAL) 17 August 2000 (2000-08-17) the whole document ---	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3 (in part), 11-24 (in part)

Present claims 1-3, 11-24 relate to an extremely large number of possible compounds. In fact, the claims contain so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely those parts where the sugar in the compound of claim 1 is as defined in claim 2 and the masked phosphate in the compound of claim 1 is as defined in claim 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/14203

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [X] Claims Nos.: 1-3 (in part), 11-24 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9629336 A	26-09-1996	AU 707196 B2	08-07-1999
		AU 5009496 A	08-10-1996
		CA 2215190 A1	26-09-1996
		EP 0820461 A1	28-01-1998
		WO 9629336 A1	26-09-1996
		JP 11506419 T	08-06-1999
		NZ 303711 A	25-02-1999
		US 6455513 B1	24-09-2002
GB 2309969 A	13-08-1997	AU 712310 B2	04-11-1999
		AU 1610397 A	22-08-1997
		CA 2243679 A1	07-08-1997
		EP 0885235 A1	23-12-1998
		WO 9728176 A1	07-08-1997
		JP 2000504009 T	04-04-2000
		US 6239159 B1	29-05-2001
WO 0047591 A	17-08-2000	AU 2671300 A	29-08-2000
		BR 0008135 A	19-02-2002
		CA 2362662 A1	17-08-2000
		CN 1346360 T	24-04-2002
		CZ 20012908 A3	16-10-2002
		WO 0047591 A1	17-08-2000
		EP 1150988 A1	07-11-2001
		HU 0105476 A2	29-06-2002
		JP 2002536452 T	29-10-2002
		NO 20013910 A	10-10-2001
		PL 350023 A1	21-10-2002
		TR 200102313 T2	21-03-2002